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Short-Term Outcome of Modified Ultrafiltration in Pediatric Cardiac Surgery: A Study in Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh

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Abstract **Original Research Article**

Background: Modified ultrafiltration (MUF) after cardiopulmonary bypass (CPB) in children decreases body water, removes inflammatory mediators, improves hemodynamics, and decreases transfusion requirements. The optimal target population for MUF needs to be defined. This prospective, randomized study attempted to identify the best candidates for MUF during operations for congenital heart disease. ***Objective:*** To assess the short-term outcome of modified ultrafiltration in pediatric cardiac surgery. ***Methods:*** This prospective study was conducted among the Informed consent was obtained from 60 patients with complex congenital heart disease undergoing operations with CPB during January 2014 to June 2019 in Pediatric Cardiac Surgery Department at Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh. They were randomized into a control group (n=30) of conventional ultrafiltration during bypass and an experimental group modified ultrafiltration after bypass (MUF group, n=30). Postoperative arterial oxygenation, duration of ventilatory support, transfusion requirements, hematocrit, chest tube output, and time to chest tube removal were compared between the groups stratified by age and weight, CPB technique, existence of preoperative pulmonary hypertension, and diagnosis. ***Results:*** There were no MUF-related complications. Inpatients with preoperative pulmonary hypertension, MUF significantly improved postoperative oxygenation (445 ±129 mm Hg versus control: 307± 113 mm Hg, p=0.02), shortened ventilatory support (42.9 ±29.5 hours. Patients with pre-op PH, Ventilatory Support control: 162.4 ±131.2 hours, MUF: 42.9 ± 29.5[a],p=0.04), decreased blood transfusion (red blood cells: 16.2± 18.2 mL/kg versus control: 41.4 ±27.8 mL/kg, p=0.01; coagulation factors: 5.3. ± 6.9 mL/kg versus control: 32.3±15.5 mL/kg, p=0.01), and led to earlier chest tube removal. In patients with pro-longed CPB (>120 minutes), MUF significantly reduced the duration of ventilatory support (44.7±37.0 hours versus 128.7±133.4 hours, p=0.04). No significant differences were observed between MUF and control patients for any parameter in the presence of ventricular septal defect without pulmonary hypertension or tetralogy of Fallot. We also observed that the ultrafiltrate volume (ml) was comparatively smaller in modified ultrafiltration. There was significant difference in both groups. ***Conclusion:*** Modified ultrafiltration after CPB is safeand decreases the need for homologous blood transfusion, the duration of ventilatory support, and chest tube placement in selected patients with complex congenital heart disease. The optimal use of MUF includes patients with preoperative pulmonary hypertension and patients who require prolonged CPB.

Keywords: MUF significantly, ventilatory support, CPB.

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INTRODUCTION

Cardiopulmonary bypasses (CPB), particularly in pediatric cardiac surgery, significantly contributes to the development of postoperative morbidity. Pediatric patients due to CPB develop a systemic inflammatory response syndrome (SIRS) which increases total body water and may result in multi-organ dysfunction.Ultrafiltration (UF), during and after CPB, is an important tool which mitigates these side effects. Standard pediatric UF techniques are conventional ultrafiltration (CUF) and modified ultrafiltration (MUF). CUF implies UF during CPB, whereas MUF is performed after CPB discontinuation. Most significant characteristics of CPB that trigger SIRS are hypothermia, hemodilution, anticoagulation,

nonpulsatile blood flow, and exposure of blood to nonendotheilazed surfaces [1, 2]. A number of adverse effects are associated with the use of cardiopulmonary bypass (CPB) in children [3, 4]. There is an increase in capillary permeability thatleads to an overall increase in total body water and edema formation [5]. Pulmonary compliance and gas transfer are decreased and myocardial edema may result in diastolic dysfunction.Conventional efforts to reduce the detrimental effects of capillary leak syndrome after CPB include reducing circuit volumes, optimizing bypass techniques, various anti-inflammatory therapies, postoperative diuresis, and peritoneal dialysis. The technique of modified ultrafiltration (MUF) is an alternative method to reduce the adverse effect of CPB in pediatric patients.Cardiac surgery is associated with the increase of vascular permeability, fluid retention causing interstitial edema and decline in the respiratory and cardiovascular function. It leads to an increase in postoperative mortality and morbidity. Several strategies have been described in the attempt of minimizing the inflammatory response, such as minimally invasive surgeries, anti-inflammatory drugs and hemofiltration during surgery. The latter modality, more specifically, the modified ultrafiltration, was described by Elliot *et al*., and initially used in paediatric patients [3-6]. Ultrafiltration can ameliorate the effects of cardiac surgeries by removing free water and inflammatory mediators (low molecular weight preferably). This technique uses a semi-permeable membrane with a positive trans membrane hydrostatic pressure gradient. It has been demonstrated that it can decrease the deleterious effects of cardiopulmonary bypass and is routinely used worldwide. There are two different methods of ultrafiltration. Conventional ultrafiltration (CUF) is the first one and is performed during CPB. One positive aspect of this technique is its ease of use and that cardiopulmonary bypass need not be prolonged. On the other hand, sometimes it can only achieve moderate haemoconcentration because the amount of eliminated fluid is limited by the level contained in the venous reservoir. The second procedure is called modified ultrafiltration (MUF). This is performed after cardiopulmonary bypass is finished and is independent of the volume contained in the circuit. This difference enables MUF to provide more effective haemoconcentration, removing more free water and a higher potential to reduce inflammatory mediators. The downside of this method is that it extends the duration of patient exposure to non-endothelial surfaces because of the prolonged time of the technique (after the ends of CPB, usually 15 minutes are needed before removal of cannula). So, this study was planned to see the impact of modified ultrafiltration on early morbidity along with onhemodynamic, pulmonary functions after adult cardiac operations [5, 7].

OBJECTIVE

To assess the short-term outcome of modified ultrafiltration in pediatric cardiac surgery.

METHODS AND MATERIALS

This prospectivestudy was conducted among 60 children with complex congenital heart disease who were undergoing operations with the use of CPB Pediatric Cardiac Surgery unit during January 2014 to June 2019 at Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh. Informed consent was obtained from the parents of each child. Using a random number table, we assigned 60 patients to one of two groups as follows: control group (n =30) undergoing conventional ultrafiltration during CPB and experimental group (n =30) having modified ultrafiltration (MUF) after CPB (MUF group). The preoperative diagnoses and patient characteristics for each group are depicted in Tables 1 and 2. Except for weight, no significant differences were observed between the groups with respect to diagnoses and demographics. Preoperative evaluation was performed by cardiac catheterization in all patients with ventricular septal defect (VSD), complete atrioventricular canal and ventricular septal defect, and by echocardiography in all patients with total anomalous pulmonary venous connection. Preoperative PH was defined as a systolic pulmonary/ systemic arterial pressure ratio 60% by catheterization. The 9 patients not catheterized had systemic or super-systemic pulmonary arterial pressure as estimated by echocardiography. Operative management was standardized during the time frame of this study. Cannulation was accomplished by use of the ascending aorta and separate caval cannulas were inserted through the superior vena cava and invention vena cava. After 300 U/kg of heparin was infused, CPB was instituted at a flow rate of 2.4 L. min $^{-1}$ m^{-2}, and the perfusate was cooled to 28° to 32°C in 75% of patients (moderate hypothermia group). Pump prime consisted of ringers lactate solution, Albumin 25% 20ml/100ml solution, methylprednisolone 30mg/kg. Whole blood sufficient to maintain hematocrit 20%-24% was added as needed. Arterial partial pressure of carbon dioxide was managed by the stat method and $NaHCO_3$ was added when the base excess was>-3. Cold crystalloid cardioplegic solution was injected at a total volume of 15 mL/kg. Topical hypothermia was added. The infusion of cardioplegic solution was repeated at 25 minute intervals or sooner if electrical activity was noted.

Details of Technique

Modified ultrafiltration was performed after coming off CPB and before the reversal of heparin, usually through the haemofilter and with negative suction applied to the ultrafiltrate. Flow of MUF was maintained around 10-15 ml/kg/min, with a mean duration of 15 min. With the aortic cannula in place, cardioplegia was flushed using the haemofilter. After filling the patient with a correct preload for

haemodynamic stability, MUF was started, using the aortic cannula as inflow onto the oxygenator and the haemofilter, whilst the arterial filter was clamped. Blood then reached the cardioplegia system, where the heat exchanger maintained it around 37 degrees. From here, it was returned to the patient through the IVC cannula towards the right atrium. Simultaneously, all the volume contained in the CPB circuit was haemoconcentrated and the patient was transfused.After achieving haemostasis and chest closure, patients was transferred to intensive care unit. In the intensive care unit, patients were monitored according to ICU protocol. Discharge criteria from the intensive care unit included a complete wean from all vasoactive and inotropic infusion, extubating without pulmonary support and no evidence of major organ failure. Discharge criteria from hospital included stable rhythm, no supplemental oxygen requirement, ambulation and tolerance of oral intake.

Measurement of hemodynamics was including heart rate, mean arterial pressure and central venous pressure. Pulmonary function consisted of oxygen index, arterial to alveolar oxygen tension (a/A ratio) and alveolar arterial oxygen gradient (A-aDO2), calculated according to alveolar gas equation based on arterial blood gas analysis. All patients after anaesthetic induction was monitored by invasive blood pressure in the left radial artery and the orotracheal tube was connected to Respiratory and hemodynamic data will be collected during: anaesthetic induction, 15 minutes after discontinuing CPB and immediately preceding MUF, immediately following MUF, 24 hours of postoperative and 48 hours of postoperative. The oxygengradient (DO2), oxygen consumption (VO2), oxygen extraction (EO2), pulmonary shunt (Qs/Qt), alveolus-arterial difference (Aadifference) and oxygenation index was calculated. The haematocrit, serum lactate dosage, platelet counting, white blood cell counting, creatinine dosage, activated partial thromboplastin time (R) and international normalized ratio of prothrombin time (INR) was acquired from the results of the main laboratory of our institution. The data relating to bleeding, amount of fresh frozen plasma, platelet rich plasma andpacked cell transfused per patient was filed from the intensive care unit report. Physiological parameters were compared in both groups. The continuous variables were expressed as mean and standard deviation, and the categorical variables were expressed as proportions. Discrete variables were evaluated by chi-square test and continuous variables by unpaired Student t-test. All statistical tests were based on two-tailed probability and a p-value <0.05 was considered statistically significant [6].

STATISTICAL ANALYSIS

Data were analyzed with the "SPSS" software package 20. The difference of postoperative arterial oxygenation, duration of ventilatory support, transfusion requirements, chest tube output, and time to chest tube removal were compared between the groups using a Mann-Whitney U test. Hematocrit, systemic and pulmonary arterial pressures between the groups were determined by analysis of variance for repeated measures. The incidence of blood transfusion were compared between the groups by Fisher's exact test. All values were expressed as mean 6 standard deviation of the mean.

RESULTS

This study was two postoperative death for the 60 operations for an overall operative mortality of 1%. The cause of death was low output syndrome. There were total 60 patients were studied prospectively. There were no differences among the groups in terms of baseline demographic parameter, previous history, and preoperative functional status.This patient died after 5 days of extracorporeal membrane oxygenation support, and was excluded from analysis in this study thus leaving 60 patients to be analyzed in this study. Noother death occurred 3 months postoperatively in this series. There were no MUF-related complications. No patients required mediastinalreexploration for bleeding. However, 1 patient from the control group underwent mediastinalreexploration to control chylothorax.Immediate Postoperative Changes in Hemodynamicsin the MUF group, systemic pressure improved from a mean of 69.5 ±14.2 mm Hg to 85.1±15.8 mm Hg.

Table-1: Preoperative Diagnosis (n=60)

Characteristic	Control	MUF
CAVC	5	5
TAPVC	2	4
VSD	15	14
TOF	8	7
Total	30	30

CAVC=complete atrioventricular canal; TAPVC=total anom- alous pulmonary venous connection; TOF =tetralogy of Fallot; VSD=ventricular septal defect.

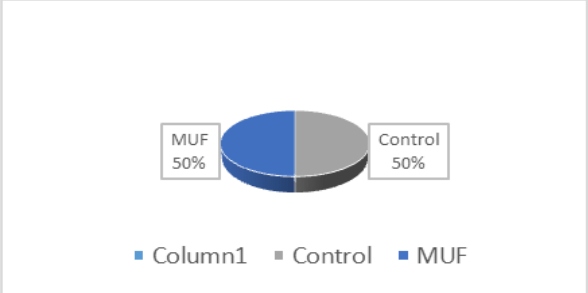

Fig-1: Preoperative Diagnosis of the patient's case

Table-2: Patient Demographics (n=60)

Characteristic	Control(n=30)	MUF(n=30)	P=Value
Sex (M/F)	13/17	16/14	0.32
Age (mo)	30.1±42.2	17.72±0.7	0.07
Weight (kg)	9±3	8.5±3.5	0.03
Preop PH	13(44%)	15(50%)	0.68
CPB time (min)	139.5±51.8	128.0±47.4	0.25
Prolonged CPB(>120 min)	18(60%)	17(58%)	
Ao clamp time (min)	80.1±43.0	67.5±39.7	0.13

Ao= aortic; CPB = cardiopulmonary bypass; MUF = modified ultrafiltration; PH = pulmonary hypertension

Table-3: Duration of Ventilatory Support (hours) (n=60)

Group	Control	MUF
Overall	98.7±116.8	34.6 ± 33.0[a]
Patients with pre-op PH	162.4±131.2	42.9 ± 29.5[a]
Prolonged CPB(>120 min)	128.7±133.4	44.7 ±37.0[a]

[a]p<0.04 versus control.
CPB = cardiopulmonary bypass; MUF = modified ultrafiltration; PH = pulmonary hypertension

Table-4: Requirements of Packed cell and Coagulation Factors (Fresh Frozen Plasma, Platelets, and PRP) (n=60)

Product	Overall		Patients with pre-op PH		Prolonged CPB(>120 min)	
	Control (mL/kg)	MUF(mL/kg)	Control(mL/kg)	MUF(mL/kg)	Control(mL/kg)	MUF(mL/kg)
Packed cell	27.1±23.9	13.3 ±14.6[a]	41.4 ±27.8	16.2± 18.2[a]	28.8 ±24.1	16.6± 16.5[c]
Coag Factors (FFP, Platelet, PRP)	19.8±20.1	4.2 ±6.9[a]	32.3± 15.5	5.3 ±6.9[a]	21.7 ±23.1	5.8 ± 8.1[a]

[a]p<0.01 versus control,b p=0.09 versus control, c p=0.03 versus control. Coag = coagulation; FFP = fresh frozen plasma; MUF = modified ultrafiltration; PRP= platelet rich plasma; PH = pulmonary hypertension; RBC = red blood cell.

In the MUF group, hematocrit was improved from 20.3%± 4.1% to 31.9% ± 5.2% immediately after modified ultrafiltration. However, changes in hematocrit after operation were similar between the groups. Total cavopulmonary connection, alveolar-arterial oxygen gradient was significantly better in the MUF group compared with controls in patients with preoperative PH (445±129 mm Hg versus 307±113 mm Hg, p=0.02). There were no significant differences between the groups in arterial oxygenation overall or in other subgroups of patients. Duration of ventilatory support was significantly longer in controls compared with MUF patients overall, and in the groups of patients with preoperative PH, those with prolonged CPB (Table-2). No significant differences were observed between the groups in patients with VSD without PH or tetralogy of Fallot, (34.4± 41.2 hours versus control: 52.78±7.5 hours, p=0.41).Requirements for packed cell and coagulation factors (fresh frozen plasma, platelets, and PRP) were significantly lower in the MUF patients compared with controls in our overall experience and in neonates, as well as those groups of patients with preoperative PH or prolonged CPB (Table-2).

Table-5: Requirements of Red Blood Cells and Coagulation Factors (Fresh Frozen Plasma, Platelets, and Cryoprecipitate), Stratified by Bypass Techniques (n=60)

Product	Moderate/Mild Hypothermia			Deep Hypothermia (DHCA)		
	Control (mL/kg)	MUF (mL/kg)	p Value	Control (mL/kg)	MUF (mL/kg)	p Value
RBC	24.8 ± 23.1	10.4 ± 9.5	0.0007	37.1 ± 26.0	20.8 ± 20.8	0.09
Coag Factors (FFP, Platelet, PRP)	16.9 ± 17.7	3.3 ± 6.8	0.0001	32.8 ± 26.1	5.8 ± 7.0	0.0006

Coag= coagulation; FFP =fresh frozen plasma; MUF= modified ultrafiltration; PRP= platelet rich plasma; RBC=red blood cell.

Only 14% of control patients (4 of 30) did not require red blood cell transfusion, whereas 36% of patients (11 of 30) in the MUF group were free from postoperative red blood cell transfusion (p=0.018 by Fisher's exact test). Moreover, 70% (21 of 30) of MUF patients did not require coagulation factor transfusion,

whereas only 24% (7 of 30) controls were free from transfusion of coagulation factors (p=0.001) by Fisher's exact test).Blood loss was determined by the chest tube output during the first 24 hours. Although no significant differences were observed between the groups in our overall experience (MUF: 21.2 ±16.8 mL/kg per 24 hours versus control: 26.0 ± 23.7 mL/kg per 24 hours, p=0.25), MUF significantly reduced the chest tube output in patients with preoperative PH (MUF: 16.4 ± 11.2 mL/kg per 24 hours versus control: 32.1±28.9 mL/kg per 24 hours, p=0.03) and in patients who underwent CPB using moderate hypothermia (MUF: 15.9±8.8 mL/kg per 24 hours versus control: 27.2±25.9 mL/kg per 24 hours, p=0.01).

Other Clinical Observations

Time to chest tube removal was significantly longer in patients with preoperative PH (MUF: 3.2± 1.6 days versus control: 6.3 ±2.4 days, p Value 0.03). Otherwise, there were no significant differences between the groups.The length of ICU stay was significantly longer in controls compared to the MUF group (MUF: 3.8 ±3.2 days versus control: 6.9± 5.7 days, p=0.01) in the overall experience. This was also the case in patients with preoperative PH (5.1 ±4 days versus control: 9.15±.9 days, p= 0.01) and patients who required prolonged CPB (4.8 ±3.9 days versus 7.9±5.9 days, p=0.03).

DISCUSSION

Cardiopulmonary bypass in children is associated with the accumulation of water as a consequence of an inflammatory capillary leak [24]. That increase in total body water is associated with tissue edema and subsequent organ dysfunction, particularly in the heart, lungs, and brain. Previous studies have shown that MUF after CPB in children decreases body water, removes inflammatory mediators, improves hemodynamics, and decreases transfusion requirements [15, 16]. This study attempted to determine the optimal target population for MUF. In this prospective, randomized study, the most striking benefits of MUF were found in patients with preoperative PH. Modified ultrafiltration significantly improved immediate postoperative arterial oxygenation in patients without intracardiac mixing and an extracardiac conduit. Modified ultrafiltration also resulted in lower pulmonary arterial pressure. Moreover MUF patients required less homologous blood transfusion and had shorter ventilatory support. Removal of free water and use of fewer transfusions may contribute to improved pulmonary mechanics after CPB [25] and result in earlier extubation in the MUF patients. Removal of small molecule inflammatory agents including endothelin-1 (a potent pulmonary vasoconstrictor) [10], and other cytokines may also play a significant role in lowering postoperative pulmonary arterial pressure and reducing lung injury after reperfusion [14]. Cardiac surgery can facilitate the development of a systemic inflammatory response syndrome (SIRS), and can promote capillary leakage and interstitial water retention. Moreover, although this study was performed strictly in prospective fashion based on diagnosis, there were significant differences in weight and borderline differences in age between the control and MUF groups. In a smaller study, Naik and colleagues [6] found benefits of MUF only in the neonatal population, suggesting that perhaps the major effect seen in our study was attributable to that group of patients. However, in older patients (>30 days) with preoperative PH, MUF significantly reduced ICU stay (control: 9.1± 5.9 days, MUF: 5.1± 4.0 days, p5 0.01). Moreover patients with prolonged CPB times (>120 minutes), MUF required shorter ventilatory support (control: 91.5±140.4 hours versus MUF: 39.3±36.5 hours, p=0.037) and had less blood loss (control: 221 48± mL/kg versus MUF: 117± 28 mL/kg, p=0.008) after operation. In the presence of VSD without preoperative PH, or tetralogy of Fallot, no significant differences were observed between MUF and control patients for any parameter.However, the size of this group of patients is small in this study and statistical power is not adequate to make firm conclusions on these individual lesions. No MUF-related complication was observed in this study, and we believe there were several advantages of our approach. Extracorporeal physiopathological changes could lead to organ dysfunction, including multiorgan failure syndrome. This lead to an increase in probability of postoperative morbidity [9, 10]. In order to avoid these potential non-desired effects, some pharmacological interventions have been designed and used, such as steroids, aprotinin or antioxidants. Moreover, some modifications have been done to the surgery process. Ultrafiltration technique allows convective transport of liquid and low-medium molecular weight molecules due to a pressure gradient through a semi-permeable membrane. Because of this, fluid overload is avoided and it is possible to reduce interstitial fluid, achieve haemoconcentration (decrease haemodilution) and wash out inflammatory mediators, but not proteins. In the cardiac surgery background, ultrafiltration has been proven to be clinically useful [11, 12]. In the present study we studied the effects of MUF inpaediatricpatients undergoing cardiac surgery. Use of MUF resulted in decreased postoperative blood loss, as indicated by decreased chest tube blood drainage and fewer RBC units transfused. Luciani and coworkers observed that ultrafiltration has been proven to be clinically useful, either when it is performed during CPB (CUF) or just after it (MUF). They carried out prospective and randomized clinical trial of 573 patients, comparing the clinical outcomes of patients who received MUF with patients without ultrafiltration. They demonstrated that the technique is safe and also that the ultrafiltration group needs less transfusion and develops less gastrointestinal, neurological and respiratory morbidity. Mortality, although lower in the ultrafiltration group, was not significantly different compared to the control group [13]. Leyh and

colleagues studied patients scheduled for elective myocardial revascularization who were randomized to groups undergoing conventional ultrafiltration, MUF, or no ultrafiltration. They observed that reduced blood loss at 24 hours after surgery in the MUF group compared with the conventional ultrafiltration and no ultrafiltration groups. Leyh and colleagues could not elucidate the mechanism(s) for reduced blood loss. Babka *et al*., studied 60 patients undergoing CBP. They observed that there was no difference in blood loss, blood transfused and length of stay or cost of patient [14]. Our study was limited by the sample size, although we were able to show a t decrease in postoperative bleeding after MUF. The lack of randomization and a non-blind medical and nursing staff to treatments might have affected the results. In future, it would be desirable to develop a multicentre, randomized study, with an elevated number of recruited patients, to clearly elucidate the differences in clinical outcomes associated with the application of different techniques and amounts of removal fluid. The study was not designed to evaluate mortality. Thus, MUF potentially has a significant impact on reducing the cost of congenital heart operations. Further study to elucidate the impact of MUF on the cost of treatment of complex congenital heart disease is now ongoing in our institution. In conclusion, this study demonstrates that venovenous MUF is safe and decreases the need for homologous blood transfusion, duration of ventilatory support, and length of ICU stay in selected patients with complex congenital heart disease. The optimal use of MUF includes patients with preoperative PH, neonates, and patients who require prolonged CPB. Although no beneficial effect was observed in either subgroups with VSD without PH or tetralogy of Fallot, this may simply be attributable to a small sample size of each diagnostic group in this study.

CONCLUSION

Modified ultrafiltration after CPB is safe and decreases the need for homologous blood transfusion, the duration of ventilatory support, and chest tube placement in selected patients with complex congenital heart disease. The optimal use of MUF includes patients with preoperative pulmonary hypertension, neonates, and patients who require prolonged CPB of capillary leak syndrome after CPB include reducing circuit volumes, optimizing bypass techniques, various anti-inflammatory therapies, postoperative diuresis, and peritoneal dialysis is an alternative method to reduce the adverse effects of CPB in pediatric patients.

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